Subparts D–J [Reserved]

Subpart K—Bulk Drug Formulations for Repacking or for Manufacturing Use

AUTHORITY: 21 U.S.C. 357.

Subpart A—Bulk Drugs

§ 440.1a Sterile azlocillin sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile azlocillin sodium is the sodium salt of 4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[[[[(2-oxo-1-imidazolidinyl)carbonyl] amino]phenylac-etyl]amino]-[2*S*-[2α,5α,6β(*S**)]]-. It is so purified and dried that:

(i) If the azlocillin sodium is not packaged for dispensing, its azlocillin content is not less than 859 micrograms and not more than 1,000 micrograms of azlocillin per milligram on an anhydrous basis. If the azlocillin sodium is packaged for dispensing, its azlocillin content is not less than 859 micrograms and not more than 1,000 micrograms of azlocillin per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 115 percent of the number of milligrams of azlocillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 2.5 percent.

(v) Its pH in an aqueous solution containing 100 milligrams of azlocillin per milliliter is not less than 6.0 and not more than 8.0.

(vi) Its specific rotation in an aqueous solution containing 10 milligrams of azlocillin per milliliter is +170° to +200°.

(vii) It gives a positive identity test for azlocillin.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, specific rotation, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) If it is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams; and 5 packages, each containing approximately 1 gram.

(*2*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(*b*) If it is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 15 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 442.40(b)(1)(ii) of this chapter, except:

(i) *Dilute Brij 35 solution.* In lieu of the hydroxylamine hydrochloride solution described in § 442.40(b)(1)(ii)(*b*)(*1*) of this chapter, use dilute Brij 35 solution in the reference channel. Prepare dilute Brij 35 solution as follows: Place 1 milliliter of Brij 35, 30 percent solution, into a 1-liter volumetric flask containing 900 milliliters of distilled water. Swirl gently and dilute to volume slowly with distilled water. Mix well.

(ii) *Buffer.* In lieu of the buffer described in § 442.40(b)(1)(ii)(*b*)(*2*) of this chapter, use the buffer prepared as follows: Dissolve 200 grams of primary standard tris (hydroxymethyl) aminomethane in sufficient distilled water to make 1 liter. Filter before use.

(iii) *Preparation of working standard solution.* Dissolve and dilute an accurately weighed portion of the azlocillin working standard with sufficient distilled water to obtain a concentration of 1.0 milligram of azlocillin per milliliter.

(iv) *Preparation of sample solutions*—(*a*) *Product not packaged for dispensing (micrograms of azlocillin per milligram).* Dissolve and dilute an accurately weighed portion of the sample with sufficient distilled water to obtain a stock solution of 1.0 milligram of azlocillin per milliliter (estimated).

(*b*) *Product packaged for dispensing.* Determine both micrograms of azlocillin per milligram of the sample and milligrams of azlocillin per container. Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(iv)(*b*)(*1*) and (*2*) of this section.

(*1*) *Micrograms of azlocillin per milligram.* Dissolve and dilute an accurately weighed portion of the sample with sufficient distilled water to obtain a stock solution of 1.0 milligram of azlocillin per milliliter (estimated).

(*2*) *Milligrams of azlocillin per container.* Reconstitute as directed in the labeling using distilled water in lieu of the reconstituting fluid. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with distilled water to a concentration of 1.0 milligram of azlocillin per milliliter (estimated).

(v) *Calculations*—(*a*) Calculate the micrograms of azlocillin per milligram of sample as follows:

$$\text{Micrograms of azlocillin per milligram of sample} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100_{-m})}$$

where:

A_u=Absorbance of sample solution;
P_s=Potency of working standard solution in micrograms per milliliter;
A_s=Absorbance of working standard solution;
C_u=Milligrams of sample per milliliter of sample solution; and
m=Percent moisture in sample.

(*b*) Calculate the azlocillin content of the single-dose vial as follows:

$$\text{Milligrams of azlocillin per vial} = \frac{A_u \times P_s \times d}{A_s \times 1{,}000}$$

where:

A_u=Absorbance of sample solution;
P_s=Potency of working standard solution in micrograms per milliliter;
A_s=Absorbance of working standard solution; and
d=Dilution factor of the sample.

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in §436.32(b) of this chapter, using a solution containing 100 milligrams of azlocillin per milliliter.

(4) *Moisture.* Proceed as directed in §436.201 of this chapter, using the titration procedure and calculations described in paragraph (e)(2) of that section and preparing the sample as follows: Weigh the vial. Rapidly transfer a portion of the powder into the titration vessel, add the Karl Fischer reagent and restopper the vial immediately. Reweigh the vial to obtain the sample weight. A nitrogen purged glove bag or glove box should be used for preparing the sample.

(5) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams of azlocillin per milliliter.

(6) *Specific rotation.* Proceed as directed in §436.210 of this chapter, using an aqueous solution containing 10 milligrams of azlocillin per milliliter and a 1.0-decimeter polarimeter tube. Calculate the specific rotation on an anhydrous basis.

(7) *Identity.* Proceed as directed in §436.336 of this chapter.

[47 FR 53348, Nov. 26, 1982, as amended at 50 FR 1504, Jan. 11, 1985; 55 FR 11582, Mar. 29, 1990]

§ 440.2a Sterile amdinocillin.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile amdinocillin is 4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(hexahydro-1*H*-azepin-1-yl)-methylene]amino]-3,3-dimethyl-7-oxo-, [2*S*-2α,5α,6β)]-. It is so purified and dried that: